Anticoagulation for stroke prevention in atrial fibrillation: is gender important?

Gregory Y.H. Lip*, Timothy Watson, and Eduard Shantsila

Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Dudley Road, Birmingham B18 7QH, England, UK

Online publish-ahead-of-print 4 July 2006

This editorial refers to 'Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials‡ by M. Gomberg-Maitland et al., on page 1947

The presence of atrial fibrillation (AF) confers a five-fold increased risk of stroke, a figure that may rise to as high as 17 times in the presence of structural heart disease, in particular mitral stenosis. It is estimated that 15% of all strokes may be directly attributable to AF, but of greater concern is that when patients with AF have a stroke, they have a much worse outcome. Being an increasingly more prevalent arrhythmia and given the increasing mean age of the general population, AF presents a significant economic burden.

Why does AF confer such a high risk of stroke and thrombo-embolism? The loss of co-ordinated atrial contraction in AF, associated with stasis and structural (and electrical) remodelling may predispose to this. There is also accumulating evidence that AF may confer a hypercoagulable state, further promoting thrombogenesis. Perhaps equally importantly, AF is common in patients with other stroke risk factors, such as hypertension, heart failure, or diabetes mellitus, and the presence of one or more of these serves to cumulatively increase the risk of stroke.

The benefits of thromboprophylaxis in stroke prevention have been shown by good evidence from clinical trials.

Despite this strong evidence in favour of anticoagulation, there remains a reluctance to prescribe warfarin, particularly in those patient groups deemed at high risk of complications. Unfortunately, it is these very patients who are often also at higher risk of stroke. The main concern, of course, is of significant haemorrhage, but physicians tend to be poor at balancing the risk of stroke and bleeding.

Furthermore, many patients are wary about starting anticoagulation and some may pressurize the doctor into (perhaps misguided) alternative strategies. Nevertheless, the importance of thromboprophylaxis is strongly stressed in many national guidelines and risk stratification is encouraged.

As is often the case, the story is never quite so simple. There is increasing evidence that gender plays an important role in both the epidemiology of AF and the risk of stroke. The majority of studies published to date have concluded that AF is more common in men. For example, the Renfrew–Paisley study demonstrates that the prevalence of AF was eight per 1000 males and five per 1000 females. This finding is mirrored by the Framingham study, where 2.2% of men had AF compared to only 1.7% of women and that the risk of developing AF was 1.5 times greater in men than women. The natural assumption has therefore been that it would be men rather than women who would be at the greatest risk of complications.

The gender debate, in relation to AF and stroke risk, resurfaces in paroxysms. For example, the Stroke Prevention in Atrial Fibrillation (SPAF) study, Renfrew–Paisley study, and Framingham investigators found women to be at greater risk of stroke, in the context of AF. In the Framingham study, AF was associated with a 1.5-fold rate of mortality in men and a 1.9-fold risk in women. More recently, the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) study found that AF was more commonly reported in men than women (1.1 vs. 0.8%, P < .001), but their recently published gender analysis showed that non-anticoagulated women has a significantly greater annual rate of thrombo-embolic events than men [3.5 vs. 1.8%; adjusted rate ratio (RR), 1.6; 95% CI 1.3–1.9], even after correction for other stroke risk factors such as age, diabetes, etc.

Furthermore, 30-day mortality in the ATRIA study following an ischaemic stroke did not differ by sex, suggesting that the increased stroke frequency in women was not counterbalanced by the occurrence of less severe strokes. Reassuringly, the ATRIA study reported that warfarin was effective in both sexes, with a slight advantage in women compared with men (RR for thrombo-embolism, 0.4; 95% CI 0.3–0.5; and RR 0.6; 95% CI 0.5–0.8, respectively). A similar distribution of INR intensity was achieved in both sexes, and bleeding events did not differ statistically between women and men when the two cohorts were analysed (1.0 vs 1.1%; adjusted RR, 0.8; 95% CI, 0.6–1.1, respectively). Conversely, many other studies have shown...
that elderly women are less likely to be prescribed warfarin for AF. Given that women are clearly at increased risk of stroke, the reasons for this merit further consideration.

Gomberg-Maitland et al.\textsuperscript{6} report the gender analysis from the pooled analysis of the SPORTIF clinical trials. Although many may have mourned the passing of ximelagatran,\textsuperscript{9} the huge database of this contemporary clinical trial of thromboprophylaxis in AF provides many added insights into the clinical epidemiology and natural history of patients with AF, in relation to stroke prevention. Indeed, Gomberg-Maitland et al.\textsuperscript{6} found that women in the SPORTIF trials tended to be older than men, with more stroke risk factors. As expected, women had an increased risk of stroke, thrombo-embolism, and mortality. However, the rates of major bleeding were not different between the cohorts but importantly, women were less likely to have received antithrombotic therapy prior to entry, despite their clear excess risk for stroke over men. Indeed, this may perhaps reflect a fear among these patients regarding bleeding complications.

Other broad issues perhaps merit debate. First, if women with AF do worse, why might this be so? The increased age and risk factors, as well as underutilization of anticoagulation may be valid reasons, as highlighted by Gomberg-Maitland et al.\textsuperscript{6} Although female gender may independently contribute to stroke on a multivariate analysis and/or statistical modelling in some analyses, such statistical adjustments can never account for all biological and pathophysiological processes. Many patients with AF possess very limited knowledge about their cardiac condition, its consequences, and how anticoagulant treatment can benefit them, but more data are needed on gender differences. Other concomitant therapies may also contribute. For example, hormone replacement therapy has been associated with an increased risk of stroke and thrombosis-related complications and unsurprisingly, has been reported as a stroke risk factor among AF populations.\textsuperscript{10} Finally, women may respond differently to men in relation to thromboprophylaxis or to different drugs. The analysis by Gomberg-Maitland et al.\textsuperscript{6} clearly shows a higher overall event rate on anticoagulation (whether with warfarin or ximelagatran) in women compared with men and, interestingly, a significantly higher event rate in women on ximelagatran compared with warfarin.

A convincing and plausible biological reason for an increased risk of stroke and thrombo-embolism in women with AF, as well as how well women respond to thromboprophylaxis, is still needed. The new evidence-based UK National Institute for Health and Clinical Excellence (NICE) National clinical guideline for the management of AF (www.nice.org.uk) found that the evidence was 'unclear' as to whether female gender was a significant independent risk factor. Clearly, more data from prospective studies will be required.

**References**